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| 54) Title: MEDICINAL AEROSOL FORMULATION 57) Abstract A solution aerosol formulation containing a drug methylether, or a mixture thereof. | | rol phosphatide, and a propellant system containing n-butane, di |

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MEDICINAL AEROSOL FORMULATIONS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal, or topical administration 10 which are at least substantially free of chlorofluorocarbons.

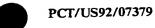
Description of the Related Art

Since the metered dose pressurized inhaler was 15 introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of 20 action and a low instance of systemic side effects. More recently, inhalation from a pressurized inhaler has been a route selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with treatment of a bronchial malady.

The metered dose inhaler is dependent upon the propulsive force of a propellant system used in its manufacture. The propellant generally comprises a mixture of liquified chlorofluorocarbons (CFC's) which are selected to provide the desired vapor pressure and 30 stability of the formulation. Propellants 11, 12 and 114 are the most widely used propellants in aerosol formulations for inhalation administration.

The aerosol formulations are generally in the form of a suspension of drug in the propellant utilizing a 35 surfactant. There are few drugs which are soluble in aerosol propellants and solution formulations have been prepared using a polar cosolvent, such as ethanol.





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European Patent No. 209547 discloses solution formulations of drugs in chlorofluorocarbon propellants in the presence of a glycerol phosphatide.

In recent years it has been established that CFC's react with the ozone layer around the earth and contribute towards its depletion. There has been considerable pressure around the world to reduce substantially the use of CFC's, and various Governments have banned the "non-essential" use of CFC's. Such "non-essential" uses include the use of CFC's as refrigerants and blowing agents, but heretofore the use of CFC's in medicines, which contributes to less than 1% of the total use of CFC's, has not been restricted. Nevertheless, in view of the adverse effect of CFC's on the ozone layer it is desirable to seek alternative propellant systems which are suitable for use in inhalation aerosols.

Various alternative propellants have been suggested for use in place of CFC's. European Patent 20 Application No. 89312270.5 discloses that 1,1,1,2tetrafluoroethane (Propellant 134a), may be employed as a propellant for aerosol formulations suitable for inhalation therapy when used in combination with a compound (hereinafter an "adjuvant") having a higher 25 polarity than Propellant 134a. The adjuvant should be miscible with Propellant 134a in the amounts employed. Suitable adjuvants include alcohols such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane, 30 pentane, isopentane, neopentane, and other propellants such as those commonly referred to as Propellants 11, 12, 114, 113, 142b, 152a 124, and dimethyl ether. Preferred adjuvants are liquids or gases at room temperature (22°C) at atmospheric pressure. 35 combination of one or more of such adjuvants with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems



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based on CFC's, allowing use of known surfactants and additives in the pharmaceutical formulations. particularly advantageous since the toxicity and use of such compounds in metered dose inhalers for drug 5 delivery to the human lung is well established.

It has been suggested that hydrocarbons, such as n-butane, isobutane, and propane be considered as CFC replacements in aerosol formulations. However, it has been found that such hydrocarbons have low densities 10 relative to the drugs in the formulations and that suspension formulations sediment rapidly and are Furthermore, the solubility of many unacceptable. drugs in these hydrocarbons is not sufficient, and solution formulations therefore do not contain suitable 15 amounts of drug.

Summary of the Invention

It has now been found that the solubility of many drugs in certain hydrocarbons and dimethyl ether may be 20 enhanced in the presence of glycerol phosphatide.

Therefore according to the present invention there is provided an aerosol formulation which contains no dispersed phase, comprising: an aerosol propellant system comprising a propellant selected from n-butane, 25 dimethylether, and mixtures thereof; a glycerol phosphatide; and a drug, in which the drug is dissolved in the composition in an amount greater than could be achieved in the absence of glycerol phosphatide.

30 Detailed Description of the Invention

The glycerol phosphatide may be any one of the following compounds; phosphatidylcholine (lecithin), phosphatidylethanolamine (cephalin), phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol, 35 or phosphatidic acid.

It has been found that drugs having at least very slight solubility in hydrocarbon propellants will

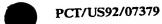


exhibit an enhanced solubility in the propellant in the presence of glycerol phosphatide. Surprisingly it has been found that glycerol phosphatides cause complete dissolution of certain drugs in n-butane and 5 dimethylether. It is postulated that this enhanced solubility is attributable to drug in true solution becoming associated with reverse micelles of the glycerol phosphatide which allows further drug to dissolve in the propellant. Thus, the solubilization 10 process is believed to be as follows:

drug ----- drug in solution ----- drug associated with reverse in propellant micelles of glycerol phosphatide

> "Micellar solubilization" solubilization"

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and the second second

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While the compositions of the invention appear visibly to be true solutions since there is no dispersed phase apparent, they are more correctly referred to as micellar solutions.

The formulations of the invention can be prepared by forming a concentrate of glycerol phosphatide with a drug and propellant. The concentrate can be formed by simple admixture with agitation and optionally under heating, e.g., 50°C, until complete dissolution of the 30 drug has been attained. The concentrate can then be mixed with the remainder of the propellant formulation.

Phosphatidylcholine is the most suitable glycerol phosphatide to use in view of its low toxicity and high drug solubilizing efficacy. Commercial grades of 35 lecithin vary widely in phosphatidylcholine content. Purified phosphatidylcholine (e.g., having phosphatidylcholine content in excess of about 90% by



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weight) is preferred for use in this invention. Phosphatidylcholine purified from soya bean lecithin is readily available commercially and suitable grades include Epikuron™ 200 (Lucas-Meyer) and Lipoid™ S100 5 (Lipoid KG). Both products have a phosphatidylcholine content in excess of 95%.

It has been found that certain drugs which are practically insoluble in hydrocarbon propellants alone can be solubilized by adding a small amount, e.g., up 10 to 5% by weight of a cosolvent, such as ethanol, to the formulation. It is postulated that the cosolvent enhances the initial solubilization step of the solubilization process. Certain commercially available forms of lecithin, e.g., Lipoid™ S45, contain ethanol 15 in addition to their phosphatidylcholine content. With lecithins of this type, the ethanol may likewise enhance drug solubilization in a formulation of the invention.

Suitable drugs for use in the invention include 20 those which exhibit at least a very slight solubility in the propellant system. In general, the drug will be in a relatively non-polar form, e.g., the form of an ester, base, or free alcohol. Highly polar ionic salts of drugs are generally less suitable since it is 25 difficult to solubilize the drug in sufficient quantity even with the presence of a small amount of cosolvent.

The drug is generally present in the formulation in an amount in the range from 0.1 to 15 mg/mL, usually from 2 to 10 mg/mL based on the total volume of the 30 formulation. Suitable medicaments include those disclosed in European Patent Application No. 89312270.5 and include, but are not limited to, albuterol, beclomethasone dipropionate, fentanyl citrate, isoprenaline, rimiterol, pirbuterol, adrenaline, 35 disodium cromoglycate (DSCG), histamine acid sulphate, morphine and its salts, ergotamine, atropine, captopril, propranolol, diazepam, glycerol trinitrate,



isosorbide dinitrate, isosorbide mononitrate, and ipratropium bromide.

The propellant system contains one or both of nbutane and dimethylether and can include copropellants 5 such as isobutane and propane. The propellant system may include minor amounts of other propellants, but preferably contains no more than 5% by weight of CFCs. More preferably the propellant system is free from CFCs.

In general, the compositions comprising drug, 10 glycerol phosphatide, and propellant system contain one to 500, preferably one to 30, more preferably 2 to 10, parts by weight drug based on 100 parts by weight glycerol phosphatide, and 0.01 to 20, preferably 0.01 15 to 10, more preferably 0.01 to 3, parts by weight glycerol phosphatide based on 100 parts by weight propellant system.

The invention will now be illustrated by the following Examples.

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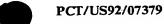
EXAMPLE 1

| | Albuterol | mg/mL 2.00 |
|----|----------------------------------|---------------|
| | Lipoid™ S100 phosphatidylcholine | 14.00 |
| 25 | n-butane | 563.00 |
| | | 579.00 |

A concentrate was prepared by combining the drug, 30 the phosphatidylcholine, and a portion of the n-butane in a pressure resistant vessel. Dissolution of this concentrate was achieved by heating for 1 hour in a water bath maintained at 55°C.

The solution was then cooled and the remainder of 35 the n-butane was added. The resulting formulation was in the form of a stable solution.





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EXAMPLE_2

| | | mq/mL |
|---|----------------------------------|--------|
| | Albuterol | 2.00 |
| | Lipoid™ S100 phosphatidylcholine | 14.00 |
| 5 | n-Butane | 125.56 |
| | Dimethylether | 502.24 |
| | · | |
| | | 643.80 |

The drug, phosphatidylcholine, and n-butane were mixed in a pressure resistant vessel to form a concentrate. Dissolution was achieved by heating for 1 hour in a water bath maintained at 55°C.

The solution was then cooled and the dimethylether

15 was added. The resulting formulation was in the form

of a stable solution.

EXAMPLE 3

| | | mq/mL |
|----|----------------------------------|--------|
| 20 | Albuterol | 2.00 |
| | Lipoid™ S100 phosphatidylcholine | 14.00 |
| | n-Butane | 113.32 |
| | Iso-butane | 339.96 |
| | Dimethylether | 113.32 |
| 25 | | |
| | | 582.60 |
| | | |

The formulation was prepared according to the general method of Example 2 and complete dissolution 30 was achieved.





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EXAMPLE 4

| | | mg/mr |
|---|---------------------------------|--------|
| | Beclomethasone Dipropionate | 1.00 |
| | Lipoid S100 phosphatidylcholine | 7.00 |
| 5 | n-Butane | 114.92 |
| , | Drivosol ^m 32* | 344.76 |
| | Dimethylether | 114.92 |
| | • | 582.60 |
| | | |

*A mixture containing 77 percent isobutane, 4 percent n-butane, and 19 percent propane by weight.

The drug, phosphatidylcholine, and a portion of

15 the dimethylether were mixed in a pressure resistant

vessel to form a concentrate. Dissolution was achieved

by agitation at room temperature.

The solution was then cooled to -40°C followed by addition of the other components of the propellant 20 system. The resulting formulation was in the form of a stable solution.

EXAMPLE 5

| | | (a) |
|----|----------------------|-------|
| 25 | Albuterol | 0.007 |
| 23 | Phosphatidylinositol | 0.050 |
| | ammonium salt | |
| | n-Butane | 0.400 |
| | n-Butane overage | 0.300 |
| 30 | | 0.757 |

The components were introduced into a polyethyleneterephthalate vial (15 mL) and a non35 metering valve was crimped in place. An n-butane overage of 0.300 g was present in the formulation to allow for evaporation in the head space in the vial.





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A solution was obtained after three hours immersion in a 55°C water bath. The formulation was allowed to stand and cool to room temperature. No precipitation or crystallization was observed.

EXAMPLE 6

| | • | <u>(a)</u> |
|-----|----------------------------|------------|
| | Albuterol | 0.014 |
| • • | 3-Sn-Phosphatidyl-L-Serine | 0.100 |
| 10 | n-Butane | 0.700 |
| | n-Butane overage | 0.300 |
| | | |
| | | 1.114 |

The formulation was prepared as in Example 5.

After immersion in the waterbath for 2 hours a solution was obtained. The formulation was allowed to stand and cool to room temperature. No precipitation or crystallization was observed.

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EXAMPLE 7

The following materials were weighed into a polyethyleneterephthalate vial and a non-metering valve was crimped in place:

| 25 | | <u>(a)</u> |
|----|---------------------------------|------------|
| | Betamethasone valerate | 0.100 |
| | Lipoid S100 phosphatidylcholine | 0.700 |
| | n-Butane | 5.600 |
| 30 | · | 6.400 |

The vial was subjected to ultrasonic energy for 30 seconds and then placed in a water bath at 55°C. After 15 minutes solubilization had been achieved; upon 35 cooling no precipitation was observed.





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EXAMPLES 8 AND 9

The following formulations were prepared:

| | mg/ml | (a) |
|----------------------------------|-----------|--------|
| Drug | 2.00 | 0.120 |
| 5 Epikuron™ 200 phosphatidylchol | ine 14.00 | 0.841 |
| n-Butane | 113.32 | 6.808 |
| Drivosol™ 32* | 339.96 | 20.423 |
| Dimethylether | 113.32 | 6.808 |
| | | |
| 10 | 582.60 | 35.000 |

*A mixture containing 77 percent isobutane, 4 percent n-butane, and 19 percent propane by weight.

15 The drug (atropine in Example 8 and captopril in Example 9) and the phosphatidylcholine were weighed into a plastic coated glass bottle which was then sealed with a non-metering valve. The required quantity of n-butane was then pressure-filled into the sealed bottle to form a concentrate. The sealed bottle was then heated for 1 hour at 55°C in a water bath. The sealed bottle was then allowed to cool to room temperature and the remaining propellants were filled into the bottle.

EXAMPLE 8

The drug, atropine (base), was solubilized within 1 hour in the concentrate and remained in solution when the remaining propellants were added.

EXAMPLE 9

The drug, captopril, was solubilized within one hour in the concentrate and remained in solution when the remaining propellants were added.

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EXAMPLES 10 AND 11

The following formulations were prepared:

| | | mg/ml | <u>(a)</u> | |
|----|-----------------------|----------|------------|---------|
| | Drug | 2.00 | 0.104) | • • |
| 5 | Epikuron™ 200 | 14.00 | 0.725) | |
| | n-Butane (20%) | 112.66 | 5.834) | concen- |
| | Ethanol (2.5%) | 14.08 | 0.729) | trate |
| | Drivosol 32 (60%) | 337.98 | 17.503 | |
| | Dimethylether (17.5%) | 98.58 | 5.105 | • |
| 10 | | <u> </u> | | |
| | | 579.300 | 30.000 | |

The formulations were prepared by weighing the drug (propranolol hydrochloride in Example 10 and 15 diazepam in Example 11), the phosphatidylcholine, and the ethanol into a glass vial, sealing the vial with a non-metering valve and pressure filling the required amount of n-butane into the sealed vial to form a concentrate. Each vial was then heated at 55°C for 2 20 hours in a water bath. The vials were allowed to cool to room temperature and the remaining propellants were filled into the vials.

The drugs both solubilized in the concentrate and remained in solution after cooling to room temperature 25 and after remaining propellants were added.

In separate tests it was not possible to achieve solubilization of the drugs in the concentrate in absence of ethanol.

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CLAIMS

- An aerosol formulation which contains substantially no dispersed phase, comprising: an aerosol propellant system comprising a propellant selected from n-butane, dimethylether and mixtures thereof; a glycerol phosphatide; and a drug, in which the drug is dissolved in the composition in an amount greater than could be achieved in the absence of the glycerol phosphatide.
 - A formulation according to Claim 1, wherein the propellant system further comprises a copropellant selected from isobutane, propane, and mixtures thereof.
- 3. A formulation according to Claim 1 or Claim 2 in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylserine, diphosphatidylglycerol, phosphatidic acid, and mixtures thereof.
 - 4. A formulation according to Claim 3 in which the glycerol phosphatide is phosphatidylcholine.
- 25 5. A formulation according to any preceding Claim in which the glycerol phosphatide is purified.
- 6. A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to 30 propellant is 0.01 to 20: 100.
 - 7. A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to propellant is 0.01 to 10: 100.

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- A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to propellant is 0.01 to 3 : 100.
- A formulation according to any preceding 5 9. Claim in which the ratio of drug to glycerol phosphatide is 1 to 500 : 100.
- A formulation according to any preceding 10 Claim in which the ratio of drug to glycerol phosphatide is 1 to 30: 100.
- A formulation according to any preceding Claim in which the ratio of drug to glycerol 15 phosphatide is 2 to 10: 100.
 - A formulation according to any preceding Claim which additionally comprises a cosolvent in an amount effective to enhance solubilization of the drug.
 - A formulation according to Claim 12 in which the cosolvent is ethanol.
- A formulation according to any preceding 25 Claim in which the drug is selected from beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and base thereof, albuterol, atropine base, and prednisolone.
- A formulation according to any one of Claim 1 30 to 13 in which the drug is selected from diazepam, lorazepam, atropine, captopril, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide, xylometazoline hydrochloride, 35 bitolterol mesylate, and lacicortone.





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- 16. A formulation according to any preceding Claim containing less than 5% by weight of chlorofluorocarbons.
- 17. A formulation according to Claim 16 which is free of chlorofluorocarbons.

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INTERNATIONAL SEARCH REPORT

| | ~~ | INTERNATIONAL SEARC | International Application No. | /US 92/07379 |
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| I. CLASSIF | ICATION OF SUBJ | LCT MATTER (If several classification syn | abols apply, indicate all)6 | |
| According t | 5 A61K9/00 | Classification (IPC) or to both National Cla | ssification and IPC | |
| II. FIELDS | SEARCHED | | | |
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| | | Documentation Searched other to to the Extent that such Documents as | han Minimum Documentation re Included in the Fields Searched ⁸ | |
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| III. DOCUM | MENTS CONSIDER | ED TO BE RELEVANT 9 | 12 | Relevant to Claim No.13 |
| Category o | Citation of D | ocument, 11 with indication, where appropria | te, of the relevant passages " | Westernt in Craim 140. |
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International Application No (CONTINUED FROM THE SECOND SHEET III. DOCUMENTS CONSIDERED TO EVANT Relevant to Claim No. Citation of Document, with indication, where appropriate, of the relevant passages 12,13 GB,A,970 027 (REVLON INC.) 16 September 1964 see claims 1,3 see page 2, line 41 - line 43 see page 2, line 63 - line 71

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

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